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Original Article

Safety of therapeutic hypothermia in children on veno-arterial extracorporeal membrane oxygenation after cardiac surgery

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Abstract *Objective:* The aim of this study was to evaluate whether the use of therapeutic hypothermia in patients receiving extracorporeal membrane oxygenation after paediatric cardiac surgery is associated with increased complication rates. *Methods:* We undertook a retrospective study to compare the complication rates and clinical course of children after cardiac surgery in two groups – extracorporeal membrane oxygenation without therapeutic hypothermia (group 1) and extracorporeal membrane oxygenation with therapeutic hypothermia (group 2). Therapeutic hypothermia was performed via the extracorporeal membrane oxygenation circuit heater–cooler device. *Results:* A total of 96 patients were included in this study (59 in group 1 and 37 in group 2). Complications were comparable between group 1 and group 2, except that more patients with therapeutic hypothermia had hypertension while on extracorporeal membrane oxygenation. Therapeutic hypothermia was not independently associated with in-hospital mortality (adjusted odds ratio 1.16, 95% CI: 0.33–4.03; p = 0.82). *Conclusion:* Therapeutic hypothermia can be safely provided to children on extracorporeal membrane oxygenation after cardiac surgery without an increase in complication rates.

Keywords: Extracorporeal life support; paediatric; outcomes; bleeding

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THE ROLE OF THERAPEUTIC HYPOTHERMIA IN critical illness is actively debated. Uncertainties abound regarding precise indications, technique, duration, and potential benefits. There is some evidence that therapeutic hypothermia may improve survival and mitigate both cardiac and brain injury, particularly after cardiac arrest. For example, in one animal study, 24 hours of extracorporeal membrane oxygenation support was performed with animals being randomised to either hypothermia (33°C) or normothermia. The hypothermia group showed improved survival as well as better cerebral and cardiac outcomes.[1] Hypothermia is also associated with improved survival and better neurodevelopmental outcomes in newborns with moderate-to-severe hypoxic ischaemic encephalopathy.[2] The American Heart Association recommends hypothermia for the treatment of neurological injury following resuscitation from out-of-hospital cardiac arrest when the initial cardiac rhythm is ventricular fibrillation.[3]

Despite potential complications such as arrhythmias,[4] coagulation dysfunction,[5] and infection,[6]

The work was performed at the Royal Children's Hospital, Melbourne, Australia.

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small case series have shown that mild therapeutic hypothermia during extracorporeal membrane oxygenation may be safe and feasible.[7–10] Some clinicians, however, remain reluctant to initiate moderate therapeutic hypothermia (33°C) after cardiac surgery because of concerns over these side-effects. Although the indications for therapeutic hypothermia after cardiac surgery are not well-defined, it might be a useful intervention in selected cases of prolonged cerebral hypoperfusion or following post-operative cardiovascular collapse. We undertook a retrospective study to compare the side-effect profile and clinical course of children after cardiac surgery in two different groups, (1) extracorporeal membrane oxygenation without therapeutic hypothermia and (2) extracorporeal membrane oxygenation with therapeutic hypothermia. Our hypothesis was that therapeutic hypothermia would not be associated with increased complications.

Materials and methods

We retrospectively reviewed the medical records of patients who received extracorporeal membrane oxygenation with or without therapeutic hypothermia after cardiac surgery between January, 2005 and December, 2011. Our institutional review board approved the study and waived the need for informed consent.

Extracorporeal membrane oxygenation protocol

The extracorporeal membrane oxygenation system consisted of a poly (2-methoxyethyl acrylate)-coated tubing; a Quadrox D (Maquet, Hirrlingen, Germany), MedosHilite LT (Medos, Stolberg, Germany), or Lilliput 2 oxygenator (Sorin, Milano, Italy); and a Rotaflow (Maquet) pump head. A description of our routine management of ventilator settings, vasoactive agents, extracorporeal membrane oxygenation flows, and anticoagulation in patients on extracorporeal membrane oxygenation have been described in detail elsewhere.[11] In brief, central cannulation was preferred in children who were recently (<14 days) post-cardiotomy. After an initial bolus of 50–100 U/kg of heparin at cannulation, heparin was titrated to maintain an activated clotting time of 160–180 seconds. Extracorporeal membrane oxygenation flows were increased to a goal of 120–150 ml/kg/min and adjusted according to preset targets. Mechanical ventilation was lowered to rest settings when adequate flows were established.

Therapeutic hypothermia

During the study period, therapeutic hypothermia was not routinely performed. Patients were cooled at the discretion of the attending physician. Therefore, patients were retrospectively assigned to two groups: group 1 in which patients were supported by veno-arterial extracorporeal membrane oxygenation only and group 2 in which patients were supported by veno-arterial extracorporeal membrane oxygenation plus therapeutic hypothermia.

With adequate sedation, therapeutic hypothermia was induced via the heater–cooler incorporated into the extracorporeal membrane oxygenation circuit as soon as patients were on support. Other medical treatment and extracorporeal membrane oxygenation management were the same, regardless of the use of therapeutic hypothermia. The goal was to achieve a core temperature of 32–33°C, monitored by an oesophageal temperature probe, within 2 hours of the decision to cool the patient. Hypothermia was maintained for 24–72 hours, and then patients were slowly re-warmed to normothermia (0.5°C every 4 hours). Temperatures above 37°C were avoided. Extracorporeal membrane oxygenation patients with spontaneous hypothermia who were promptly re-warmed to normothermia and patients on extracorporeal membrane oxygenation cooled to normothermia were allocated to group 1. Extracorporeal membrane oxygenation patients were not weaned off mechanical circulatory support before re-warming to 36.5°C.

Core temperatures were recorded every hour. Adequate hypothermia was defined as core temperature < target temperature + 0.5°C before re-warming, otherwise it was regarded as inadequate hypothermia. The following timelines were calculated: time between the primary insult (eg. cardiac arrest) and initiation of hypothermia; time required to reach the target temperature; time of adequate and inadequate hypothermia; and time needed to re-warm patients to 36.5°C.

Data collection

Demographic data, pre-extracorporeal membrane oxygenation or therapeutic hypothermia status, extracorporeal membrane oxygenation setup and management, extracorporeal membrane oxygenation- and hypothermia-related complications, and clinical outcomes were retrospectively collected. Demographic data included gender, age, body weight, paediatric index of mortality 2, and risk adjustment for congenital heart surgery-1 category. Pre-extracorporeal membrane oxygenation or hypothermia status included mechanical ventilation before extracorporeal membrane oxygenation, need for cardiopulmonary resuscitation, arterial blood gas and biochemistry results, and inotropic support immediately before extracorporeal membrane oxygenation or therapeutic hypothermia. Inotropic score was calculated based on

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the formula (doses in mcg/kg/min): Dopamine + Dobutamine + (epinephrine × 100) + (norepinephrine × 100) + (Milirone × 15).[12] A score ⩽20, >20 and ⩽40, and >40 was regarded as low, medium, and high, respectively. Extracorporeal membrane oxygenation setup and management included oxygenator type, cannulation site, circuit change, duration of support, and total blood product transfusion during extracorporeal membrane oxygenation. Therapeutic hypothermia-related complications included gastrointestinal bleeding, thrombocytopaenia, seizures, intracranial infarction or bleeding, dialysis, and infection. Extracorporeal membrane oxygenation-related complications included cannula-site bleeding, haemolysis, hypertension, inotropic support on extracorporeal membrane oxygenation, poor ventricular contractility, pneumothorax, and pulmonary bleeding. Hypertension was defined practically as the need to initiate vasodilator therapy. Poor ventricular contractility was defined qualitatively on transthoracic echocardiography by the reporting cardiologist. Outcomes included weaning from extracorporeal membrane oxygenation, survival to ICU discharge, mechanical ventilation time, ICU stay, and survival to hospital discharge. Among patients experiencing multiple extracorporeal membrane oxygenation runs, only the first run was included. Patients with extracorporeal membrane oxygenation support <24 hours were also excluded from the study.

Statistical analysis

The primary endpoint was survival to hospital discharge. Statistical analysis was carried out using Stata version 12.0 (StataCorp LP, College Station, Texas, United States of America). Normal distribution was assessed by visual inspection of standardised normal probability plots. Continuous variables were expressed as mean with one standard deviation or median (range) and were compared using Student's t-test or the Wilcoxon rank-sum test, as appropriate. Categorical variables were expressed as percentages and were compared using the χ^2 test or Fisher's exact test where numbers were small. In order to compare the difference in temperature between the two study groups (hypothermia vs. non-hypothermia) during the first 72 hours after extracorporeal membrane oxygenation initiation, repeated measures analysis of variance was used. Models were fitted using main effects for group, time, and an interaction between group and time in order to ascertain whether the groups behaved differently over time. Demographic data, pre-extracorporeal membrane oxygenation support or therapeutic hypothermia status, extracorporeal membrane oxygenation setup, management information and extracorporeal membrane oxygenation-related complications, and hypothermia-related complications were compared between the two groups with univariate analysis. Logistic regression was performed to assess the independent effect of therapeutic hypothermia on in-hospital mortality, adjusting for potential confounders including cardiopulmonary resuscitation, duration of mechanical ventilation, lactate immediately before extracorporeal membrane oxygenation, surgical complexity – using risk adjustment for congenital heart surgery-1 categories[13] – and hypertension requiring vasodilator therapy. Both base excess and pH were highly correlated to lactate; thus, only lactate was entered into the model to avoid collinearity. Due to skewed distribution, duration of mechanical ventilation was log-transformed. Zero values were replaced by 0.1 to avoid missing values generated by log-transformation. Weaning off extracorporeal membrane oxygenation, survival to hospital discharge, total mechanical ventilation time, and ICU stay were also compared between the two groups. A two-sided p value <0.05 was considered as significant.

Results

From 1 January, 2005 to 31 December, 2011, 59 patients after cardiac surgery were supported with extracorporeal membrane oxygenation, and 37 patients were supported with extracorporeal membrane oxygenation and therapeutic hypothermia. Thus, 96 patients were reviewed and included in the subsequent analysis.

Of the 96 patients, there were 49 boys (51.0%), with a median age of 0.06(0.002–17) years and a median weight of 3.7 (1.7–115) kg. The median risk adjustment for congenital heart surgery-1 category was 4 (2–6). Among all, four patients were not coded by this score: three patients who received heart transplantation and one patient who underwent Fontan takedown. Demographic data were similar between the two groups (Table 1).

Significant differences were observed in pre-extracorporeal membrane oxygenation or therapeutic hypothermia status as shown in Table 2. Generally, group 1 patients had less requirement for cardiopulmonary resuscitation and shorter ventilation times before extracorporeal membrane oxygenation support, and experienced less severe acidosis compared with group 2 patients. In group 1, extracorporeal membrane oxygenation was indicated for cardiac arrest in 17 patients, refractory low cardiac output in 21 patients, and inability to wean from cardiopulmonary bypass in 21 patients. In group 2, extracorporeal membrane oxygenation was indicated for cardiac arrest in 29 patients, refractory low cardiac output in five patients, and inability to wean from cardiopulmonary bypass in three patients. In all group 2 patients, clinicians elected to use therapeutic

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Table 1. Comparison of demographic data among two groups of post-cardiac surgery patients.

	Group 1 (n = 59)	Group 2 (n = 37)	p value
Male (n)	29 (49.1%)	20 (54.0%)	0.64
Age (years)	0.07 (0.002–17)	0.06 (0.02–16)	0.41
Weight (kg)	3.7 (1.9–115)	3.7 (1.7–65)	0.93
PIM2 score	7.34 (0.51–73.35)	3.78 (0.3–93.89)	0.12
RACHS-1	4 (2–6)	3.5 (2–6)	0.21

PIM = paediatric index of mortality 2; RACHS = risk adjustment for congenital heart surgery category
In group 1, three patients were diagnosed with cardiomyopathy. All variables except gender are presented as median (range)

Table 2. Comparison of pre-ECMO status among two groups of post-cardiac surgery patients.

	Group 1 (n = 59)	Group 2 (n = 37)	p value
CPR (n) (%)	17 (28.8%)	29 (78.4%)	<0.001
MV time (h)	19 (1–984)	41 (1–956)	0.028
pH	7.33 ± 0.14	7.16 ± 0.24	<0.001
BE (mmol/L)	− 4.6 ± 7.8	− 12.2 ± 8.5	<0.001
Lactate (mmol/L)	6.0 ± 3.6	9.2 ± 5.7	0.001
Glucose (mmol/L)	9.0 ± 3.8	9.5 ± 3.7	0.53
Creatinine (μmol/L)	50 (5–190)	51 (20–140)	0.36
Inotrope score			0.35
Low (n)	36 (61.0%)	28 (75.7%)	
Medium (n)	12 (20.3%)	5 (13.5%)	
High (n)	11 (18.6%)	4 (10.8%)	
Indication			<0.001
Cardiac arrest (%)	17 (28.8%)	29 (78.4%)	
Low cardiac output (%)	21 (35.6%)	5 (13.5%)	
Inability to wean off bypass (%)	21 (35.6%)	3 (8.1%)	

BE = base excess; CPR = cardiopulmonary resuscitation before ECMO; ECMO = extracorporeal membrane oxygenation; MV = mechanical ventilation before ECMO
Inotrope score: Dopamine + Dobutamine + (Adrenaline × 100) + (Nor-adrenaline × 100) + (Milirone × 15). Low ⩽20, Medium >20 and ⩽40, High >40.
pH, lactate, glucose, and BE are presented as mean ± standard deviation. MV time and creatinine levels are presented as median (range)

hypothermia due to concerns about cerebral hypoperfusion.

The target temperature achieved in group 2 patients was 34 (32–35)°C. The median time from primary insult to initiation of hypothermia was 1(0–30) hour. It took another 3(0–19) hours to achieve the target temperature. Patients spent a median of 46 (12–71) hours with adequate hypothermia; five patients (13.5%) spent a median of 2 (2–20) hours with inadequate hypothermia. It took a median 28(10–75) hours to re-warm the patients to 36.5°C, corresponding to a median speed of 0.11(0.02–0.21)°C/hour. Patients in group 1 had a median nadir core temperature of 35.6°C (33.6–36.2°C); seven patients (10%) experienced transient spontaneous hypothermia (<35°C) and were actively re-warmed to normothermia on extracorporeal membrane oxygenation. The analysis showed that there was a significant interaction ($p < 0.001$) between hypothermia status and time on extracorporeal membrane oxygenation. The average temperature in the hypothermia group was consistently lower than the non-hypothermia group during the first 72 hours after extracorporeal membrane oxygenation initiation (Fig 1).

Extracorporeal membrane oxygenation setup, management, and complications were comparable between group 1 and group 2, except that more patients with therapeutic hypothermia had hypertension requiring vasodilator therapy while on extracorporeal membrane oxygenation (Table 3). The duration of mechanical ventilation and intensive care were similar between treatment groups. Patients in group one tended to have higher ICU and hospital survival (Table 4).

Logistic regression analysis showed that, after controlling for ventilation time, surgical complexity, hypertension requiring vasodilator therapy, cardiopulmonary resuscitation, and lactate before extracorporeal membrane oxygenation, therapeutic

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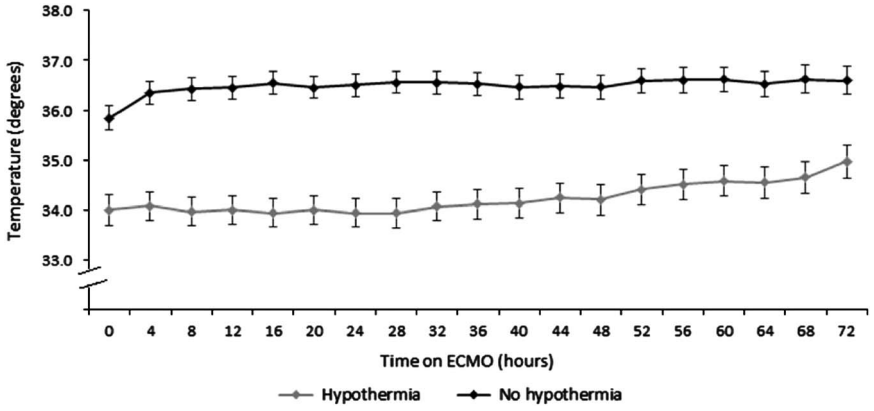

Figure 1.
Average temperatures in the hypothermia and non-hypothermia groups over time. Error bars represent 95% confidence intervals.

Table 3. Comparison of ECMO setup, management, and complications.

	Group 1 (n = 59)	Group 2 (n = 37)	p value
Oxygenator			0.70
Quadrox D (n)	44 (74.6%)	25 (67.6%)	
Medos (n)	11 (18.6%)	8 (21.6%)	
Lilliput (n)	4 (6.8%)	4 (10.8%)	
Cannulation site			0.80
Central (n)	56 (94.9%)	34 (91.9%)	
Peripheral (n)	1 (1.7%)	2 (5.4%)	
Both (n)	2 (3.4%)	1 (2.7%)	
ECMO time (h)	83 (26–332)	106 (24-367)	0.10
Circuit change (n)	6 (10.1%)	5 (13.5%)	0.75
RBC (ml/kg/h)	1.02 (0.02-5.09)	1.17 (0.12–11.75)	0.97
Platelet (ml/kg/h)	0.43 (0–3.14)	0.61 (0–11.75)	0.09
Plasma (ml/kg/h)	0.51 (0–2.28)	0.60 (0–11.75)	0.38
Cannula site bleeding* (n)	17 (28.9%)	12 (32.4%)	0.71
Pulmonary bleeding (n)	0 (0%)	1 (2.7%)	0.77
GI bleeding* (n) (%)	1 (1.7%)	0 (0%)	1.00
Intracranial bleeding (n) (%)	2 (3.4%)	0 (0%)	0.52
Haemolysis** (n)	33 (55.9%)	24 (64.9%)	0.39
Hypertension*** (n)	35 (59.3%)	30 (81.1%)	0.026
Inotropes on ECMO (n)	42 (71.1%)	27 (73.0%)	0.85
Poor contraction***** (n)	12 (20.3%)	12 (32.4%)	0.18
Pneumothorax (n)	1 (1.7%)	1 (2.7%)	1.00
Thrombocytopaenia**** (n) (%)	52 (88.1%)	36 (97.3%)	0.15
Seizures (n) (%)	1 (1.7%)	2 (5.4%)	0.56
Intracranial infarction (n) (%)	6 (10.2%)	2 (5.4%)	0.48
RRT (n) (%)	31 (52.5%)	17 (45.9%)	0.53
Haemofiltration (n) (%)	5 (8.5%)	4 (10.8%)	0.73
PD (n) (%)	26 (44.1%)	16 (43.2%)	0.94
Infection****** (n) (%)	22 (37.3%)	18 (48.6%)	0.27

ECMO = extracorporeal membrane oxygenation; GI = gastrointestinal; PD = peritoneal dialysis; RBC = red blood cell transfusion; RRT = renal replacement therapy, including haemofiltration or peritoneal dialysis
ECMO time, RBC, platelet, and plasma are presented as median (range)
*Requiring surgical or endoscopic intervention
**Free plasma haemoglobin >0.1 g/L
***Requiring vasodilator
****Platelet $< 100 \times 10^9$/L
*****Severely reduced ventricular contraction on transthoracic echocardiography
******Culture proven

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Table 4. Comparison of outcomes.

	Group 1 (n = 59)	Group 2 (n = 37)	p value
Wean ECMO (n) (%)	51 (86.4%)	26 (70.3%)	0.05
ICU discharge (n) (%)	39 (66.1%)	17 (45.9%)	0.05
Hospital discharge (n) (%)	38 (64.4%)	17 (45.9%)	0.08
MV time (h)	334 (46–1680)	288 (62–2482)	0.90
ICU stay (h)	379 (51–2906)	351 (71–2512)	0.76

ECMO = extracorporeal membrane oxygenation; MV = mechanical ventilation
MV time and ICU stay are presented as median (range)

hypothermia was not independently associated with in-hospital mortality (adjusted odds ratio 1.16, 95% CI: 0.33–4.03; p = 0.82).

Discussion

In this single-centre retrospective study, we showed that therapeutic hypothermia was not associated with increased complications, did not affect the management course of patients on extracorporeal membrane oxygenation, and was not independently related to in-hospital mortality, after controlling for pre-extracorporeal membrane oxygenation status. There was no increase in complications seen when therapeutic hypothermia was initiated in extracorporeal membrane oxygenation patients compared with those maintained at normothermia, except that more patients in group 2 developed hypertension requiring vasodilator therapy.

Both animal studies and clinical trials have shown that therapeutic hypothermia may provide neurological and cardiac protection[14–16] via several mechanisms including decreasing oxygen consumption and metabolic rate, preventing neuronal body swelling, and reducing neurotransmitter release.[17–19] Therapeutic hypothermia, targeting 32–34°C for 12–24 hours among comatose survivors of out-of-hospital cardiac arrest, has been recommended by the American Heart Association when the initial rhythm is ventricular fibrillation. Therapeutic hypothermia should also be considered in patients with other arrhythmias, after in-hospital cardiac arrest.[20] A particular study showed that cardiac arrest survivors presenting with cardiogenic shock benefited from therapeutic hypothermia in terms of myocardial performance, decreased catecholamine usage, and improved survival when compared with a historic control group of matched patients without hypothermia;[15] however, another recent study of adult unconscious survivors of out-of-hospital cardiac arrest found that therapeutic hypothermia targeting 33°C did not improve mortality or neurological outcomes compared with strictly maintained normothermia.[21]

There are few published data regarding therapeutic hypothermia for children on extracorporeal membrane oxygenation;[7,8,20] one report of five neonates showed the feasibility of providing therapeutic hypothermia combined with extracorporeal membrane oxygenation while utilising greater depth and duration of cooling (33.5°C for 72 hours).[20] Extracorporeal membrane oxygenation-facilitated cooling also maintained the target core temperature with little variance. Similarly, Horan et al[7] did not observe major adverse events while cooling five neonates to 34°C for 48 hours; however, due to the study design, adverse events and mortality were not compared between patients with hypothermia and normothermia. Furthermore, patients included in the previous studies were supported by extracorporeal membrane oxygenation either for respiratory failure or hypoxic ischaemic encephalopathy, not after cardiac surgery with the attendant risks of bleeding. Whether therapeutic hypothermia leads to better long-term neurological outcomes in children with cardiac arrest or refractory circulatory failure after cardiac surgery is unknown, but this may be clarified by an ongoing clinical trial. This study is designed to recruit >900 patients across 37 different centres, with an estimated date of completion of September, 2015 (ClinicalTrials.gov Identifier: NCT00880087).

Some limitations of our study should be acknowledged. First, this was a single-centre, retrospective study. Second, this was primarily a safety study and data on long-term survival and neurodevelopmental outcomes were not examined. Third, hypothermia was not performed or instituted by protocol. Fourth, although the incidence of bleeding was similar between the two groups, the time interval between surgery and the initiation of extracorporeal membrane oxygenation was not recorded. Patients unable to be weaned off bypass after surgery have a different risk of bleeding than patients placed on extracorporeal membrane oxygenation for cardiac arrest 24–48 hours or more after surgery. Patients with therapeutic hypothermia underwent a longer duration of mechanical ventilation and it was possible that they were more temporally remote from surgery, with

a consequently lower risk of bleeding. Finally, the sample size may have been inadequate to detect significant differences in infrequent complications and outcomes between the treatment groups.

In conclusion, therapeutic hypothermia can be safely provided to children on extracorporeal membrane oxygenation after cardiac surgery without an apparent increase in complication rates.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (National Health and Medical Research Council, Australia) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees of the Royal Children's Hospital, Melbourne, Australia.

References

1. Ao H, Tanimoto H, Yoshitake A, Moon JK, Terasaki H. Long-term mild hypothermia with extracorporeal lung and heart assist improves survival from prolonged cardiac arrest in dogs. Resuscitation 2001; 48: 163–174.
2. Tagin MA, Woolcott CG, Vincer MJ, Whyte RK, Stinson DA. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. Arch Pediatr Adolesc Med 2012; 166: 558–566.
3. ECC Committee, Subcommittees and Task Forces of the American Heart Association. American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2005; 112: 1–203.
4. Wu ET, Huang SC, Chi NH, et al. Idioventricular rhythm induced by therapeutic hypothermia. Resuscitation 2008; 76: 471–473.
5. Dirkmann D, Hanke AA, Gorlinger K, Peters J. Hypothermia and acidosis synergistically impair coagulation in human whole blood. Anesth Analg 2008; 106: 1627–1632.
6. Flores-Maldonado A, Medina-Escobedo CE, Rios-Rodriguez HM, Fernandez-Dominguez R. Mild perioperative hypothermia and the risk of wound infection. Arch Med Res 2001; 32: 227–231.
7. Horan M, Ichiba S, Firmin RK, et al. A pilot investigation of mild hypothermia in neonates receiving extracorporeal membrane oxygenation (ECMO). J Pediatr 2004; 144: 301–308.
8. Ichiba S, Killer HM, Firmin RK, Kotecha S, Edwards AD, Field D. Pilot investigation of hypothermia in neonates receiving extracorporeal membrane oxygenation. Arch Dis Child Fetal Neonatal Ed 2003; 88: F128–F133.
9. Guenther U, Varelmann D, Putensen C, Wrigge H. Extended therapeutic hypothermia for several days during extracorporeal membrane-oxygenation after drowning and cardiac arrest two cases of survival with no neurological sequelae. Resuscitation 2009; 80: 379–381.
10. Mizobuchi M, Nakamura S, Muranishi H, et al. Hypothermia with extracorporeal membrane oxygenation for sudden cardiac death and submersion. Am J Emerg Med 2010; 28: e1–e4.
11. Maclaren G, Butt W, Best D, Donath S, Taylor A. Extracorporeal membrane oxygenation for refractory septic shock in children: one institution's experience. Pediatr Crit Care Med 2007; 8: 447–451.
12. Gaies MG, Gurney JG, Yen AH, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatric Crit Care Med 2010; 11: 234–238.
13. Jenkins KJ, Gauvreau K, Newburger JW, et al. Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 2002; 123: 110–118.
14. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002; 346: 549–556.
15. Zobel C, Adler C, Kranz A, et al. Mild therapeutic hypothermia in cardiogenic shock syndrome. Crit Care 2012; 40: 1715–1723.
16. Che D, Li L, Kopil CM, Liu Z, Guo W, Neumar RW. Impact of therapeutic hypothermia onset and duration on survival, neurologic function, and neurodegeneration after cardiac arrest. Crit Care Med 2011; 39: 1423–1430.
17. Hutchison JS, Doherty DR, Orlowski JP, Kissoon N. Hypothermia therapy for cardiac arrest in pediatric patients. Pediatr Clin North Am 2008; 55: 529–544.
18. Walker PA, Harting MT, Baumgartner JE, Fletcher S, Strobel N, Cox CS Jr. Modern approaches to pediatric brain injury therapy. J Trauma 2009; 67: S120–S127.
19. Zwischenberger JB, Kirsh MM, Dechert RE, Arnold DK, Bartlett RH. Suppression of shivering decreases oxygen consumption and improves hemodynamic stability during postoperative rewarming. Ann Thorac Surg 1987; 43: 428–431.
20. Massaro A, Rais-Bahrami K, Chang T, Glass P, Short BL, Baumgart S. Therapeutic hypothermia for neonatal encephalopathy and extracorporeal membrane oxygenation. J Pediatr 2010; 157: 499–501.
21. Nielsen N, Wetterslev J, Cronberg T, et al.. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013; 23: 2197–2206.